

REMARKS

I. The Invention

The present invention relates to the surprising discovery that a broad and effective anti-tumor immunity can be achieved in a patient when inactivated tumor cells and bispecific or trispecific antibodies capable of specifically binding the tumor cells, T cells, and Fc receptor-bearing effector cells are administered separately in a time-staggered fashion, *i.e.*, the administration of tumor cells is prior to the administration of the antibodies, or *vice versa*, by a time interval ranging from 1 to 48 hours.

II. Claim Amendment

Claims 1-23 were originally filed and claims 24-36 were added subsequently. Upon entry of the present amendment, claim 1 is amended to improve clarity, correct a typographic error, and provide proper antecedent basis. The language "wherein there is a time interval between the administration of (1) (tumor cells) and the administration of (2) (bispecific or trispecific antibody)" finds support in the specification, *e.g.*, on page 2, lines 4-5. Claim 17 is amended to replace the recitation of an "inducible antigen" by reciting a surface antigen being present on a tumor cell but absent or present in an insufficient number on a non-tumor cell, which finds support in the specification, *e.g.*, page 14, line 7, to page 17, line 6, and particularly on page 16, lines 20-24. Claims 19 and 21 are amended to ensure appropriate antecedent basis. Claim 26 is amended to recite "1-4 hours," which finds support in original claim 3. New claims 37 and 38 are added to recited the number of tumor cells being administered, which finds support in the specification, *e.g.*, in the table on page 18 (rows 3 and 4). No new matter is introduced.

III. Amendment to the Specification

The specification is amended to provide priority information and to delete the reference to claim 1 on page 11, line 30, which the Examiner objected to in the Office Action of October 20, 2004. The amendment to the specification adds no new matter.

IV. Claim Objection

The Examiner objected to claim 26 for failure to further limit the subject matter of a previous claim from which it depends. Claim 26 depends from claim 25, which recites "1-6 hours." As amended, claim 26 now recites "1-4 hours" instead of "1-6 hours." The objection to claim 26 is thus overcome.

V. Claim Rejections

A. 35 U.S.C. §112, Second Paragraph

Claims 1-36 were rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse the rejections, particularly in light of the present claim amendment.

"A tumor cell" in claim 1

The Examiner held claims 1-36 indefinite for reciting "a tumor cell" in claim 1 (b) as it is unclear whether it refers to the autologous tumor cell or the allogeneic tumor cell or some other tumor cell. Claim 1 has been amended to recite "said autologous tumor cell or said allogeneic tumor cell." This rejection is thus obviated.

"The interval" in claim 3

The Examiner also rejected claim 3 and its dependent claims for reciting "the interval" without any precedent in claim 1. As amended, claim 1 recites "wherein there is a time interval between the administration of (1) and the administration of (2)." Applicants submit that a proper antecedent basis is now established. The withdrawal of this rejection is requested.

"Inducible" and "uninduced state" in claim 17

Claim 17 and its dependent claims were rejected for reciting "inducible" and "uninduced state (normal state)," as the Examiner asserted that it is unclear what the "induced state" or "uninduced state" is, and that it is also unclear what an "inducible" antigen is or what induces it. As amended, claim 17 now recites "wherein said surface antigen is absent from non-tumor cells or is present in an amount insufficient for destruction of said non-tumor cells by the

antibody." Since the phrases the Examiner objected to have been deleted from claim 17 and its dependent claims, Applicants submit that this indefiniteness rejection is moot.

The withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

B. 35 U.S.C. §103

Claims 1-36 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Berd (U.S. Patent No. 6,458,369) in view of Lindhofer *et al.* (a) (*Blood* 88:4651-4658, 1996), Lindhofer *et al.* (b) (U.S. Patent No. 6,551,592), Multihoff *et al.* (*Int. J. Cancer* 61:272-279, 1995), and Jedlitschky *et al.* (U.S. Patent No. 6,235,785). Applicants respectfully traverse the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

The pending claims are directed to a method for inducing a specific immunity against tumor cells by administering to a patient: (1) autologous tumor cells or allogeneic tumor cells of the same tumor type following treatment to prevent the tumor cells' survival after reinfusion; and (2) intact bispecific and/or trispecific antibodies capable of binding to a T cell, to at least one antigen on the tumor cell, and to Fc receptor-positive cells. The inactivated tumor cells and the bispecific or trispecific antibodies are administered with a time interval in between, regardless of the order in which the tumor cells and the antibodies are administered.

In contrast, the Berd reference relates to compositions comprising hapten-modified tumor cells and the use of such compositions for eliciting anti-tumor immunity in a patient. The reference describes the inactivation of the tumor cells by irradiation to prevent their revival after being administered to a patient, and also describes the co-administration of this tumor cell-containing composition with other therapeutic modalities including antibodies

(column 9, lines 42-62). The manner of such co-administration is described as "together or consecutively" (column 9, line 52).

The Lindhofer (a) reference relates to the use of bispecific antibodies targeting operationally tumor-specific antigens in leukemia patients following bone marrow transplant. The Lindhofer (b) reference relates to a method for inducing an anti-tumor immunity in a patient by redirecting T cells to tumor cells via the action of a bispecific antibody, which is capable of concomitant binding of a T cell, a tumor cell, and an Fc receptor-bearing effector cell. These two references do not teach or suggest the co-administration of inactivated tumor cells and the bispecific antibodies in a patient, let alone the administration of the tumor cells and antibodies at a time interval.

The Multihoff reference reports the expression of heat shock protein (HSP) 72 and 90 on the surface of certain human tumor cells but not found on normal cells. The Jedlitschky references relates to the use of mitomycin C as a chemtherapeutic agent. These two references thus are relevant only to the dependent claims of this application, as they do not provide the missing limitations of claim 1.

Applicants first contend that not all limitations of claim 1 are provided by the cited references. For example, the Examiner has not pointed out where in the cited references one might find the limitation that there should be a time interval between the administration of the inactivated tumor cells and the bispecific or trispecific antibodies. Although the Berd reference used the word "consecutively," which could be broadly construed as describing two events taking place not exactly at the same moment in time. Yet, this is not inherently the same as "in a time-staggered manner." According to Webster's New Collegiate Dictionary, the word "consecutive" means "following one after the other in order *without a gap*." This definition directly contradicts the meaning of "in a time-staggered manner" and "there is a time interval" as recited in claim 1. Applicants thus submit that it has not be established that all claim limitations are provided by the cited references.

Even if all limitations could be found in the cited references, Applicants contend that the references, when viewed together, would not provide a suggestion or motivation in the

art for one skilled artisan to combine these limitations. In particular, it remains to be identified where in the cited references might there be a suggestion for a delayed administration of a bispecific or trispecific antibody following the administration of inactivated tumor cells (or *vice versa*). In fact, when these references are viewed together, if any suggestion could be found, it would be one that suggests having the inactivated tumor cells and the bispecific or trispecific antibody administered to a patient *simultaneously*. This is because the Lindhofer (b) references describes the induction of an anti-tumor immunity by the action of a bispecific antibody--its binding *simultaneously* to a tumor cell, a T cell, and an Fc receptor-bearing effector cell. Thus, the cited references actually tend to teach away from the present invention.

Moreover, even if all limitations could be found in the cited references and there were a suggestion to combine the limitations, there would still lack a reasonable expectation of success in making such a combination. The basis of eliciting a tumor-specific immunity as described by Lindhofer (b) is the action of a bispecific antibody to bring a tumor cell, a T cell, and an Fc receptor-positive effector cell into a close vicinity. The success of this very action requires the simultaneous presence of the tumor cells and the antibodies, which is precisely the reason why it was a surprising discovery when the present inventors recognized that administration of inactivated tumor cells and bispecific or trispecific antibodies in a time-staggered fashion can effectively induce an anti-tumor immune response.

Taken together, Applicants submit that no *prima facie* obviousness has been properly established. The withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

C. Double Patenting

Claims 1-36 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-24 of copending application USSN 10/378,218.

Applicants submit that the Examiner should withdraw the provisional double patenting rejection and allow the claims pending in the present application. According to the

MPEP §822.01, “[i]f the “provisional” double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent...” This is precisely the case in the present application, as the only other rejections, the obviousness rejection and the indefiniteness rejection, have been overcome in light of the present claim amendment and above discussions. On the other hand, USSN 10/378,218 has not been allowed. Thus, Applicants respectfully request that the Examiner withdraw the provisional double patenting rejection and allow the pending claims in the present application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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